INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
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# The Effect of Psoriasis on Diastolic (Dys)Function – A Pilot Echocardiographic Study

**Ana Rita da Silva Veiga**

Dissertação de Mestrado Integrado em Medicina

Artigo de Investigação Médica

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Abstract

**Purpose**

Recent studies have established psoriasis as an independent risk factor for the development of cardiovascular disease. The aim of this study was to evaluate, with clinical, analytical and imaging methods, the effects of the systemic proinflammatory state induced by psoriasis on cardiac remodelling and evaluate Diastolic Dysfunction (DD) as an early marker of cardiovascular involvement.

**Methods**

This study enrolled 38 consecutive psoriasis patients (47,5 years, 68,4% males). Clinical information and evaluation of inflammatory markers were collected. Diastolic function was assessed by two-dimensional transthoracic echocardiography and speckle-tracking.

**Results**

This exhaustive description of statistically relevant data, and its variation according to the widely accepted diastolic dysfunction markers, found that in patients with both LA maximum volume index >34 mL/$m^2$ and LV GLS >-20%, the average PASI was highest, as well as hsCRP values. In this study, 60% of patients presented a value above 34 mL/$m^2$ and 51,4% presented LV GLS >-20%. E/A ratio below 0,75 was found in 10,8%, 8,1% had values above 1,5 and 44,4% had DT greater than 220 ms.

**Conclusion**

Echocardiography analysis, particularly with STE shows promising prospects in early identification of diastolic dysfunction in psoriatic patients. Also, hsCRP may have a role in detecting low grade inflammatory states and predict long-term repercussions of chronic inflammatory states.

**Keywords**

Psoriasis, Systemic Inflammation, Diastolic Dysfunction, Echocardiography Transthoracic, HFpEF

Resumo

**Objetivo**

Hodiernamente, a psoríase é considerada um fator de risco independente para o desenvolvimento de doenças cardiovasculares. O objetivo deste estudo foi avaliar, recorrendo a meios clínicos, analíticos e imagiológicos, os efeitos do estado pro-inflamatório sistémico induzido pela psoríase no *remodelling* cardíaco e analisar a Disfunção Diastólica como um marcador precoce do envolvimento cardíaco.

**Materiais e Métodos**

Foram incluídos sequencialmente 38 doentes psoriáticos (47,5 anos, 68,4% homens). A informação clínica e análise dos parâmetros analíticos foram colhidas na consulta e por amostras sanguíneas. A função diastólica foi avaliada através do ecocardiograma transtorácico, recorrendo a STE.

**Resultados**

A descrição exaustiva dos parâmetros estatisticamente relevantes e a sua variação de acordo com os marcadores de disfunção diastólica amplamente aceites permitiu concluir que, nos doentes com volume indexado aurícula esquerda >34 mL/m$^2$ e GLS do ventrículo esquerdo >-20%, o PASI médio foi mais elevado, bem como os valores médios de hsCRP. Neste estudo, 60% dos doentes revelaram a volume indexado aurícula esquerda >34 mL/m$^2$ e 51,4% apresentaram GLS do ventrículo esquerdo >-20%. E/A inferior a 0,75 foi observado em 10,8% dos doentes, 8,1% apresentaram valores superiores a 1,5 e 44,4% apresentou DT maior que 220 ms.

**Conclusões**

A avaliação ecocardiográfica, particularmente por STE, revela perspetivas promissoras no que à identificação precoce de disfunção diastólica em doentes com psoríase concerne. Do mesmo modo, a hsCRP poderá representar um papel na deteção de estados inflamatórios de baixo grau e predição de repercussões a longo prazo deste estado inflamatório crónico.

**Palavras-Chave**

Psoríase, Inflamação Sistémica, Disfunção Diastólica, Insuficiência Cardíaca com Fração de Ejeção Preservada, Ecocardiograma Transtorácico

Abbreviations/Acronyms

**BMI** Body Mass Index

**BP** Blood Pressure

**BSA** Body Surface Area

**C3** Complement Component 3

**DD** Diastolic Dysfunction

**DT** Deceleration Time

**EF** Ejection Fraction

**FS** Fractional shortening

**GLS** Global Longitudinal Strain

**HbA1c** Glycated hemoglobin

**HDL** High-Density Lipoprotein

**HEPA** Health Enhancing Physical Activity

**HFPEF** Heart Failure with Preserved Ejection Fraction

**hsCRP** High-Sensitive C-Reactive Protein

**ICD** Implantable Cardioverter Defibrillator

**IL** Interleukin

**IPAQ** International Physical Activity Questionnaire

**LA** Left Auricular

**LDL** Low-Density Lipoprotein

**LV EDV/ESV** Left Ventricular End-Diastolic/End-Systolic Volume

**LV** Left Ventricle

**NT-proBNP** N-terminal pro-B-type Natriuretic Peptide

**PACS** Peak Atrial Strain before Atrial Contraction

**PALS** Peak Atrial Strain at the End of Ventricular Systole

**PASI** Psoriasis Area and Severity Index

**PsA** Psoriatic Arthritis

**QoL** Quality of Life

**SD** Standard Deviation

**SPSS** Statistical Package for the Social Sciences

**STE** Speckle-Tracking Echocardiography

**TNF-α** Tumor Necrosis Factor α

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## 1. Introduction

Psoriasis is a chronic, immune-mediated and disabling inflammatory disease, with systemic involvement and great burden on both patients' quality of life (QoL) and health care systems. Registration of psoriasis cases is not compulsory, which means that its exact incidence is difficult to determine in the general population. Nevertheless, recent studies reported an incidence rate between 78.9/100,000 and 230/100,000 person-years in the adult population.[1] The reported prevalence of this disease in countries ranges between 0,09% and 11,4%. [2] According to a 2000 study in a Portuguese sample estimated a prevalence of 1,9%.[3] There is evidence to suggest that the prevalence of psoriasis may be increasing.[4] The variation in prevalence and severity is influenced by important factors, including age, geography and ethnicity.[1] Even though psoriasis is associated with low mortality rates, it has a great morbidity.

Psoriasis can occur at any age. However, some studies suggested that its onset can be bimodal with the first peak of the disease between 16 and 22 and the latter between 57 and 60 years of age. This disease has an equal sex distribution[5], but is epidemiologically more relevant in caucasians.

The etiology of psoriasis remains unclear, however there is evidence that different endogenous or environmental triggers like infection, mild trauma, systemic drugs (lithium, antimalarials and nonsteroidal anti-inflammatory drugs), sunburn, obesity and stress initiate or worsen this multifactorial syndrome in genetically prone individuals. Risk factors are recognized, including family history and environmental risk factors, such as smoking, stress, obesity, and alcohol consumption.[1]

Psoriasis involves the skin and nails, with localized or generalized lesions, mostly symmetrical, sharply demarcated, red papules and plaques, and usually covered with white or silver scales.[2] The most frequently reported symptoms connected to psoriasis include scaling of the skin in 92%, pruritus in 72%, erythema in 69% fatigue in 27%, swelling in 23% and in 20% burning or bleeding.[2]

Recent studies have suggested that there is an overexpression of various proinflammatory cytokines (Interleukin (IL)-1, IL-6, IL-8, IL-12, IL-15, IL-17-20, IL-22, IL-23), TNF-α and interferon-γ, inflammatory markers (C3, C4) and adipokine's system disorders not only in skin lesions, but in the entire organism as well. Therefore, these individuals are at a great risk of developing different systemic comorbidities including psoriatic arthritis, diabetes mellitus, obesity, hypertension, coronary heart disease[6], liver disease[7], inflammatory bowel disease[8], lymphoma and depression. Patients diagnosed with psoriasis have an increased burden of subclinical conditions such as atherosclerosis, vascular inflammation, endothelial dysfunction[9] and higher levels of serum lipids, including triglycerides and total cholesterol.[10] The greater

severity of psoriasis has been associated with an enhanced oxidative stress and dyslipidemia, implying that the risk of cardiovascular events may be higher in severe psoriasis.[11]

Different pathophysiological mechanisms can be responsible for the association between psoriasis and cardiovascular disease, such as the high prevalence of cardiovascular risk factors in psoriasis patients or the systemic proinflammatory response induced by psoriasis. Furthermore, psoriasis has been established as an independent risk factor for cardiovascular disease.[12]

Recent studies have been ascertaining the involvement of a systemic proinflammatory state induced by various non-cardiac comorbidities, as a main determinant of Diastolic Dysfunction (DD) and Heart Failure with Preserved Ejection Fraction (HFPEF). The circulating levels of inflammatory cytokines, such as interleukin 6 (IL-6), tumor necrosis factor α (TNF-α) and pentraxin 3[13, 14], can cause coronary microvascular endothelial inflammation and lead to the decrease of nitric oxide bioavailability, cyclic guanosine monophosphate and protein kinase G activity in adjacent cardiomyocytes.[15] These reactions favour hypertrophy development and stiff cardiomyocytes, because of hypophosphorylation of the cytoskeletal protein titin[16], which ultimately may lead to concentrically remodelled Left Ventricle (LV) with DD.[13] The peripheral endothelial dysfunction is independently correlated with future cardiovascular events.[17]

DD is defined as an abnormality of the left ventricle to relax and/or to fill with an adequate blood volume, and is an independent risk factor for the development of heart failure and long term mortality[18]. Subclinical DD is common within the population, with a prevalence up to 25% [19], particularly amongst older, hypertensive, diabetic and obese people, although some may remain asymptomatic and don’t even develop further heart failure.

It is plausible to think that also in the systemic proinflammatory state due to psoriasis, DD can be an early marker of cardiovascular involvement and heart failure risk. Although patients are well informed about their skin lesions, they have insufficient knowledge of their risk of atherothrombotic disease and metabolic syndrome.[20] Hence, early identification and management of subclinical changes in myocardial structure and function, and their determinants, as well as other comorbidities, can be particularly important in psoriatic patients. This allows a more efficient and effective clinical practice, an increase patients' quality of life, a reduction of costs associated with therapeutics and an improve the success of established treatments.

Through this investigation and with the aid of available clinical, analytical and imaging methods, we pretend to evaluate patients with psoriasis and infer about their inflammatory state, cardiovascular risk factors and cardiac function, particularly diastolic function.

## 2. Methods

This study is a cross-sectional institutional investigation and there will be included a sequential sample of patients with psoriasis evaluated in the Dermatology Department consult of *Centro Hospitalar do Porto*. All participants provided written informed consent to participate in the investigation.

### 2.1 Patients

The study group included 38 individuals. In this analysis, we included patients with moderate-to-severe psoriasis above the age of 18. Individuals presenting with cardiovascular disease, such as previous cardiovascular disease, ischemic heart disease, valvulopathy, heart failure, cardiac dysrhythmia, coronary artery bypass surgery, coronary angioplasty, valvuloplasty, pacemaker or Implantable Cardioverter Defibrillator (ICD) or any cardiothoracic surgery, were excluded from this study due to the higher likelihood of introducing further biases.

### 2.2 Clinical Evaluation

All patients were submitted to clinical interview to collect data on sex, age, current smoking status, International Physical Activity Questionnaire (IPAQ) short form for physical activity[21], family history of cardiovascular disease, comorbidities or ongoing medication. Regarding psoriasis, information on family history, disease duration, diagnosis of psoriatic arthritis (PsA) and use of biologic therapy was gathered. Besides, height, weight, abdominal perimeter, blood pressure (BP), cardiac frequency and body mass index (BMI) were measured during consultation.

Psoriasis severity was graded according to the gold standard score[22, 23] Psoriasis Area and Severity Index (PASI) score. PASI is a combined score consisting of a measurable evaluation of the plaque's degree of erythema, induration, and desquamation, based on four anatomical areas (head, arms, trunk and legs), weighted according to the area's proportion of the body and assigns a final score which ranges from 0 to a theoretical maximum of 72. To diminish subjectivity, the PASI was evaluated by the same dermatologist in all patients.

Regarding the categorization of the variables for ensuing statistical evaluation, IPAQ was divided in inactive, minimally active and Health Enhancing Physical Activity (HEPA active)[24]; family history of cardiovascular disease was considered present when first and/or second degree family members were affected; diabetes *mellitus*, dyslipidemia, hypertension, depression and/or ongoing medication counted for the presence of comorbidities; abdominal perimeter was divided in below or above 88 cm for females and below or above 120 cm for males; systolic BP was classified in

below or above 140 mmHg and diastolic BP in below or above 90 mmHg;[25] BMI included 4 categories (< 18,5 kg/m$^2$ underweight; 18,5-24,99 kg/m$^2$ normal range; 25-29,99 kg/m$^2$ overweight; >30 kg/m$^2$ obese).[26]

About psoriasis, family history was considered positive when first and/or second degree family members were affected; psoriasis duration was divided in decades; presence or absence of previous diagnosis of PsA; use of biologic therapy or not; psoriasis' severity was graded as PASI≤10 or PASI>10[23];

### 2.3 Laboratory Evaluation

Blood samples were collected from the subjects at the time of their clinical evaluation, and total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, apolipoprotein B, glucose, glycated haemoglobin (HbA1c), insulin, N-terminal pro-B-type natriuretic peptides (NT-proBNP), complement component 3 (C3) and high sensitive C-reactive protein (hsCRP) were measured.

These variables were categorized for statistical purposes, according to the most recent guidelines for clinical practice[27]: total cholesterol in below or above 200 mg/dL, LDL in below or above 100 mg/dL, HDL on females was divided in below or above 48 and on males in below or above 40, triglycerides in below or above 150 mg/dL, apolipoprotein B in below or above 100 mg/dL[27], HbA1c in below or above 6,5%, C3 in below or above 135 mg/dL and hsCRP in below or above 3 mg/L.

### 2.4 Echocardiography Protocol

All patients were submitted to detailed Transthoracic Echocardiography assessment, by a single experienced cardiologist, using an ultrasound system (Siemens Acuson SC2000). Images were digitally stored for posterior offline analysis. The exams were screened for adequate quality imaging to perform Speckle-Tracking Echocardiography (STE) analysis, subsequently those studies with poor imaging quality were excluded (n=1). Cardiac chamber volumes and dimensions were measured according to current recommendations.[28] Diastolic function was assessed according to the 2016 European Echocardiography Association and American Society of Echocardiography Consensus Criteria on Diastolic Function Evaluation[29]. Each measure was performed in triplicate and the mean value was used for analysis and a minimum of three cardiac cycles were recorded. All values were indexed to body surface area.

LV volumes were determined using the modified Simpson's method using apical 2 and 4 chambers views (Figures 1 and 2) at an end-systolic and end-diastolic frames and was indexed to Body Surface Area (BSA) to estimate LV EDVi and LV ESVi. Systolic function was assessed by calculating the Ejection Fraction (EF), using the same method and by analysing systolic myocardial annular tissue velocity (S' septal, S' lateral and S' mean). For statistical purposes, LV EDVi was categorized as above or below 74 mL/m$^2$ for men and 61 mL/m$^2$ for women and LV ESVi as above or below 31 mL/m$^2$ for men and 24 mL/m$^2$ for women; LV EF was divided in below or above 52% for men and below or above 54% for women. Mitral valve inflow measurements, such as early filling velocity (E), late filling velocity (A), E/A ratio and early filling deceleration time (DT) were assessed by pulsed wave Doppler.

From LA speckle tracking analysis (Figure 3), we extracted LA phasic volumes, such as: pre-A wave LA volume, maximum and minimum LA volumes. LA function indexes were calculated using these values and validated formulas. LA reservoir function was evaluated using LA emptying fraction as [(maximum LA volume - minimum LA volume) / maximum LA volume x 100] and LA expansion index as [(maximum LA volume - minimum LA volume) / minimum LA volume x 100]. LA conduit function was determined using LA passive emptying volume as (maximum LA volume - pre-A wave LA volume), LA passive emptying fraction as [(maximum LA volume – pre-A wave LA volume) / maximum LA volume]. LA booster pump function using LA active emptying fraction [(pre-A wave LA volume - minimum LA volume) / pre-A wave LA volume], and LA active emptying volume (pre-A wave LA volume - minimum LA volume). From the average of the strain curves of all segments we evaluated peak LA strain at the end of ventricular systole (PALS), peak atrial strain before atrial contraction (PACS), Systolic Strain Rate; Early Diastole Strain Rate; Late Diastole Strain Rate. LA passive emptying strain was then calculated as (PALS - PACS), which is a measure of LA conduit function. Two-dimensional STE-derived Left Auricular Longitudinal Strain (LALS) was calculated using average deformation. LALS was categorized in above or below 11,5%.[30]

### 2.5 Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences 24 (SPSS). Continuous variables are expressed as Mean ± Standard Deviation (SD), non-normally distributed variables as Median and Interquartile Range and categorical variables are reported as frequency and respective proportion (%).

# 3. Results

## 3.1 Patients characteristics

41 psoriasis patients were initially included, however 4 dropped out due to unavailability of attending the echocardiogram. The final study group counted for 38 patients, 68,4% (n=26) of whom were males with a median age of 47,5 (P25 38,8; P50 47,5; P75 56,3) years old and 36,8% were current smokers. The mean BMI was 27,6±4,5 kg/m$^2$; 55,3% of patients were overweight and 23,7% were obese. High abdominal perimeter was found in a total of 50% and 21% presented hypertension. HbA1c above 6,5% was observed in 3,4 %.

Regarding psoriasis, the mean PASI presented at consultation was 3,2±3,5; 94,7% had PASI <10 and 5,3% had PASI >10. The disease duration was up to 20 years in 52,6%. 92,1% of patients were on biologic therapy, which included ustekinumab, etanercept, secukinumab, infliximab and adalimumab. Posterior PsA diagnosis was referred in 44,7% of patients. The study group demographic and clinical characteristics can be consulted in Table 1.

## 3.2 Analytic variables

The mean values for lipid profile were 117±41 mg/dL for LDL, HDL 52±13 mg/dL, total cholesterol 196±41 mg/dL, triglycerides 114±72 mg/dL, apolipoprotein B 102±22 mg/dL. 64,5% had LDL values >100 mg/dL; 25,8% had HDL values <48 mg/dL for females or <40 mg/dL for males; 38,7% had total cholesterol values >200 mg/dL; 16,1% had triglycerides values >150 mg/dL; 55,2% had apolipoprotein B values >100 mg/dL.

Regarding the inflammatory markers C3 and hsCRP, the mean value for the first was 115,33±21,5 mg/dL and 3,6±3,9 mg/L for the latter. 13,8% had levels of C3 >135 mg/dL and 38% had hsCRP values >3 mg/L. The mean NT-proBNP value was 40,4±38,4 pg/mL. The analytic patients' characteristics can be consulted in Table 2.

## 3.3 Echocardiographic variables

This study included patients with preserved ejection fraction (mean left ventricular ejection fraction 58±3%), with a mean 9,97±1,8 mm septal wall thickness, 8,99±1,6 mm posterior wall thickness. The average LV EDVi and LV ESVi values were 52,77±34,65 mL/m$^2$ and 19,07±4,51 mL/m$^2$, respectively.

Regarding diastolic function evaluations, the mean E velocity was 71,7±12,3 cm/s, A 69,8±13,1 cm/s, DT 222±55,6 ms and E/A ratio 1,08±0,32. E/A ratio below 0,75 was found in 10,8% and 8,1% had values above 1,5. DT was greater than 220 ms in 44,4% patients.

The average medial e' was 10,5±2,7 cm/s, lateral e' 13,7±4 cm/s and an average e' of 12,1±3,3 cm/s. 18,4% (n=7) presented lateral e' < 10cm/s and 8,1% (n=3) presented medial e' < 7 cm/s. The respective medial E/e' was 7,2±1,7, lateral E/e' was 5.5±1,3 and the average E/e' 6,3±1,4. No patient presented average E/e' > 13.

STE-derived LA strain and volumes are exhaustively described below and can be consulted in Table 3. The LA maximum atrial volume's mean was 69,8±21,6 mL, LA pre-A wave atrial volume 37±16,4 mL and the LA minimum atrial volume was 18,2±9,4 mL. The mean LA maximum volume index was 36,7±10,2 mL/m$^2$ and 60% presented a value above 34 mL/m$^2$.

Concerning the reservoir LA function, mean LA emptying fraction was 74,5±8,1 and the mean LA expansion index was 359,5±158,9. About the conduit LA function, the LA passive emptying volume was 31,6±12,9 mL and respective LA passive emptying fraction was 47,6±16,3; the PALS-PACS, passive emptying strain, mean value was 32,2±17,1. Regarding booster pump LA function, the LA active emptying volume was 19±8,9 mL and the LA active emptying fraction was 51,9±11. The mean PALS was 51,3±18,6 % and the mean PACS value was 19,5±7,8 %; PALS-PACS mean value was 32,2±17,1. The mean systolic strain rate was 1,6±0.5; the mean early diastole strain rate was -1,6±0,6 and the mean late diastole strain rate was -1,4±0,8. The mean LV GLS was -18,8±5,3 % and 51,4% (n=18) presented LV GLS >-20%. The echocardiographic patients' characteristics can be consulted in Table 3.

### 3.4 Clinical and analytical variables according to the presence of echocardiographic markers of DD

The Clinical and analytical characteristics vary among the groups with positive echocardiographic markers of DD. E/e' ratio was excluded from further analysis, because it was less than 14 in all patients and therefore statistically irrelevant.

It should be noted that the average age value is higher when the LV GLS >-20% and a LA maximum volume index >34 mL/m$^2$, and so is the mean PASI and systolic BP. In contrast, the average BMI, abdominal perimeter and diastolic BP was higher in the group with LV GLS >-20%. On the other hand, the mean disease evolution was higher in the group with LA maximum volume index >34 mL/m$^2$ (see Table 4).

About the analytical variables, there are also different patterns associated. The HDL mean value was lower and the LDL mean value was higher where the two criteria met, as for the total cholesterol, apolipoprotein B and hsCRP. The average triglycerides and C3 values were higher in the group with LV GLS >-20%, whereas the NT-proBNP mean value was higher in the group with LA maximum volume index >34 mL/$m^2$ (see Table 5).

## 4. Discussion

Psoriasis has a substantially high prevalence and requires lifelong topic and/or systemic therapy.[31] However, the information regarding echocardiographic parameters in psoriasis patients is not profuse. It is very important to identify and manage patients with psoriasis, particularly those with underlying cardiovascular risk factors and/or metabolic syndrome[10], since psoriasis has been consistently described as an independent risk factor for cardiovascular disease.[12, 32] Echocardiography analysis, particularly STE, offers several advantages, specifically it evaluates LV functions more objectively and quantitively and is not subject to EF limitations. Also, this analysis is angle-independent, reproducible and quantitative, so the utility of this examination is further increased.

LV DD is usually the result of an abnormal LV relaxation with or without reduced resting forces and early diastolic suction, and increased LV chamber stiffness, which increase cardiac filling pressures. DD is common in the population, with some studies suggesting a prevalence in general population of 20,8% mild DD, 6,6% moderate DD and 0,7% severe DD. Hence, DD is often not accompanied by recognized heart failure and is established in recent studies as an independent risk factor for the development of heart failure and marked increase in all-cause long term mortality.[19] Moreover, filling patterns in the elderly resemble those observed in mild diastolic dysfunction in younger patients, and, so, age should be taken into account when evaluating diastolic function variables.[33] HFpEF, which results from a complex interplay between genetic, neurohormonal, inflammatory, and biochemical changes acting on cardiac myocytes and the cardiac interstitium, is typically characterized by the presence of diastolic dysfunction.

Several studies have recently reiterated echocardiographic changes in relation to systolic and /or diastolic function in psoriasis patients. Ahlehof, *et al*. (2016), prospectively studied 18 severe psoriasis patients treated with biologic therapy and compared myocardial function at baseline and after three months of treatment. The study group demonstrated an improvement in myocardial function (E/e' and GLS), in addition to the improvement of the PASI.[34] Atas, *et al*. (2015), assessed left atrial volume and function in psoriasis patients and healthy controls through conventional, tissue Doppler and 3D echocardiography. Although there were no significant differences between these groups, psoriasis patients had a higher incidence of left ventricular diastolic dysfunction and higher LA phasic volumes (LA maximum, minimum, passive stroke and passive emptying fraction) and impaired LA mechanical function (LA active emptying fraction, total emptying fraction, expansion index and active stroke volume).[35] Örem, et al. (2013) assessed biochemical and echocardiographic markers in 31 psoriasis patients and healthy controls and firstly described LV asynchrony as independent associated with psoriasis.[36] Gullu et al. (2013) studied 36 psoriasis patients and 56 healthy controls and coronary flow reserve is

decrease in the psoriasis group and was significantly and inversely correlated with disease duration, PASI score and hsCRP.[37] Simsek, et al. (2013) compared 94 psoriasis patients and 51 healthy controls and concluded that psoriasis patients have significant echocardiographic abnormalities, namely longer transmitral DT and isovolumetric relaxation time, and that electrocardiographic findings, such as greater P wave dispersion and QT dispersion correlated with disease duration. [38] Biyik, *et al.* (2006), investigated the incidence and severity of echocardiographic and clinical abnormalities in patients with different types of psoriasis and concluded that echocardiographic abnormalities, particularly left ventricular diastolic dysfunction, were significantly more frequent in patients with psoriasis, but also LV hypertrophy, LV wall motion abnormalities, mitral valve and tricuspid valve prolapse. [32] It is not to be despised that, in some cases, diastolic dysfunction occurs in patients without classic cardiovascular risk factors.[39]

On the other hand, the fact that therapeutic interventions suppressing the systemic proinflammatory process in psoriasis can reduce coronary microvascular dysfunction[40] and has a potentially beneficial effect on subclinical cardiovascular disease signs[41], corroborates, in some way, the abovementioned investigations. Recent studies have concluded that TNF-α inhibitors treatment ameliorates CMD in patients with established psoriasis not responding to long-term conventional therapy and thus suggest that a therapy specifically targeted against inflammation can positively affect coronary microvascular function.

Therefore, the present study is in line with the described literature, representative of the state of the art. Since our study group has very homogenous characteristics, it was not possible to divide and test the causality of certain parameters, such as psoriasis severity, biological therapy or disease duration. Thus, since it is a pilot study, it is more pertinent to make an exhaustive description of the statistically relevant data, and its variation according to the widely accepted diastolic dysfunction markers, and integrate it in the light of the most recent literature.

A high prevalence of cardiovascular disease risk factors was found in this study group, namely high abdominal perimeter, obesity, hypertension, diabetes mellitus and lipid profile abnormalities in psoriasis patients.

Regarding psoriasis markers, the mean evolution of the disease was highest in patients with LA maximum volume index >34 mL, suggesting that the cumulative exposure to this proinflammatory state may play a role in the development of DD.

Amongst biomarkers of myocyte stress, ventricular NT-proBNP synthesis is markedly increased in the failing heart and, compared to BNP, it has a longer half-life and is biologically inert.[42] Although the increase in NT-proBNP levels is less pronounced in HFNEF, higher plasma NT-proBNP levels are shown to be associated with greater severity of diastolic dysfunction in patients

with HFNEF and are strong predictors of mortality and hospitalizations.[43] Recently, some studies have proven that NT-proBNP concentrations were significantly higher in psoriasis patients and there is a positive correlation between this marker and psoriasis duration.[44] The present study describes a great increase in NT-proBNP values in patients with LA maximum volume index >34 mL when compared to the average. Nonetheless, further investigation is mandatory to validate NT-proBNP as a useful biomarker of CV disease.

Inflammatory biomarker levels may be a measure of factors driving LV remodelling in HFNEF. hsCRP is produced in the liver in response to stimulation of various cytokines, mostly IL-6.[42] hsCRP is a sensitive marker and is applied to predict and diagnose low-grade inflammatory conditions. Furthermore, hsCRP has been established as an independent predictor of prognosis in heart failure and can provide additional information for the risk stratification, as well as the response of HF patients to treatment[45]. This study refers a higher hsCRP mean in patients with both LA maximum volume index >34 mL and LV GLS >-20%. As for C3, the mean value was highest in patients with LV GLS >-20%.

The ratio of the peak early mitral inflow velocity (E) over the early diastolic mitral annular velocity (e′) has gained wide acceptability in routine clinical practice[29] as an echocardiography marker of diastolic dysfunction. In the present study, the E/e' value was normal in every single patient and therefore was not useful in this discussion. Alternatively, other indirect measures of DD were significantly abnormal in this study group, as is the case with the E/A ratio that was below 0,75 in 10,8% and above 1,5 in 8,1%; and DT that was greater than 220 ms in 44,4% patients.

Although there is no recommended universal normal range of values for LV GLS, due to considerable differences among vendors and software packages, a peak GLS in the range of -20% can be expected in healthy individuals and the lower absolute value below this, the more likely it is to be abnormal[29], which was the case for 47,4% of patients in this study.

*Limitations of the Study*

This investigation lacks the power and randomization that only large and randomized study groups and matched control subjects can provide. Secondly, follow up data is necessary to establish prognostic and progression significance of LV subclinical diastolic dysfunction.

All patients in this study had moderate-to-severe psoriasis, though they may have presented low PASI at consultation, this is because they were controlled by biological treatment. Besides, the fact that some patients were medicated for other comorbidities may have influenced the values of certain parameters, such as serum lipid values, BP measurements and inflammation markers,

undercovering the true values, since it has been demonstrated that control of these comorbidities can have a positive impact on cardiovascular disease. The presence of potential adverse effects of systemic antipsoriatic drugs may also contribute to the observed associations.

## 5. Conclusion

In conclusion, echocardiography analysis, particularly with STE shows promising prospects in early identification of diastolic dysfunction in psoriatic patients. Together, in patients with LA maximum volume index >34 mL and LV GLS >-20%, the average PASI was highest, as well as age values. Also, hsCRP may have a role in detecting low grade inflammatory states and predict long-term repercussions of chronic inflammatory states since a higher hsCRP mean was found in patients with both LA maximum volume index >34 mL and GLS >-20%.

However, further research is required to support the abovementioned premises and identify effective interventional strategies capable of delaying the inevitability of these repercussions resulting from this proinflammatory state.

## 6. Bibliography


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## 7. Tables

Table 1. Demographic and Clinic Patients' Characteristics

| Characteristic | Value |
|---|---|
| Age, years | 47,5 |
| Male, % | 68,4 |
| PASI | 3,2 ± 3,5 |
| Evolution Psoriasis, years | 21 ± 13,7 |
| Biologic Therapy, % | 92,1 |
| Psoriatic Arthritis, % | 44,7 |
| Current Smoker, % | 36,8 |
| Inactive, % | 76 |
| BMI, $kg/m^2$ | 27,6 ± 4,5 |
| Body Surface Area, $m^2$ | 1,9 ± 0,2 |
| Abdominal Perimeter, cm | 97 ± 12 |
| Systolic BP, mmHg | 128 ± 15 |
| Diastolic BP, mmHg | 79 ± 9 |

*PASI, Psoriasis Area and Severity Index; BMI, Body Mass Index; BP, Blood Pressure.*

Table 2. Analytic Patients' Characteristics

| Characteristic | Value |
|---|---|
| LDL, mg/dL | 117 ± 41 |
| HDL, mg/dL | 52 ± 13 |
| Total Cholesterol, mg/dL | 196 ± 41 |
| Triglycerides, mg/dL | 114 ± 72 |
| Apolipoprotein B, mg/dL | 102 ± 22 |
| NT-proBNP, pg/mL | 40,4 ± 38,4 |
| Complement Component 3, mg/dL | 115,3 ± 21,5 |
| High Sensitive C-Reactive Protein, mg/L | 3,6 ± 3,9 |
| HbA1c, % | 5,3 ± 0,4 |

*LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; C3, Complement Component 3; HsCRP, High-Sensitive C-Reactive Protein; HbA1c, Glycated hemoglobin.*

Table 3. Echocardiographic Patients' Characteristics

| *Characteristic* | *Value* | *Characteristic* | *Value* |
|---|---|---|---|
| Septal wall thickness, mm | 9,97 ± 1,8 | LA Maximum Atrial Volume, mL | 69,8 ± 21,6 |
| Posterior wall thickness, mm | 8,99 ± 1,6 | LA Pre-A Wave Atrial Volume, mL | 37 ± 16,4 |
| LV EDVi, mL/ $m^2$ | 52,8 ± 34,7 | LA Minimum Atrial Volume, mL | 18,2 ± 9,4 |
| LV ESVi, mL/ $m^2$ | 19,1 ± 4,5 | LA emptying fraction | 74,5 ± 8,1 |
| LV EF, % | 58 ± 3 | LA expansion index | 359,5 ± 158,9 |
| FS, % | 37,5 ± 6,5 | LA passive emptying volume, mL | 31,6 ± 12,9 |
| E, cm/s | 71,72 ± 12,3 | LA passive emptying fraction | 47,6 ± 16,3 |
| A, cm/s | 69,77 ± 13,08 | LA active emptying volume, mL | 19 ± 8,9 |
| DT, ms | 222 ± 56 | LA active emptying fraction | 51,9 ± 11 |
| E/A | 1,08 ± 0,317 | PALS, % | 51,3 ± 18,6 |
| Medial e', cm/s | 10,541 ± 2,667 | PACS, % | 19,5 ± 7,8 |
| Lateral e', cm/s | 13,7 ± 4 | PALS - PACS, % | 32,2 ± 17,1 |
| Average e', cm/s | 12,1 ± 3,3 | Systolic Strain Rate | 1,6 ± 0.5 |
| Medial E/e' | 7,2 ± 1,7 | Early Diastole Strain Rate | -1,6 ± 0,6 |
| Lateral E/e' | 5.5 ± 1,3 | Late Diastole Strain Rate | -1,4 ± 0,8 |
| Average E/e' | 6,3 ± 1,5 | LALS, % | -18,8 ± 5,3 |

*LV Left Ventricular; LV EDV/ESV Left Ventricular End-Diastolic/End-Systolic Volume; FS Fractional shortening; DT Deceleration Time; LA Left Auricular; PALS Peak Atrial Strain at the End of Ventricular Systole; PACS Peak Atrial Strain before Atrial Contraction; LALS Left Auricular Longitudinal Strain.*

Table 4. Demographic and Clinical Data According to Echocardiographic Characteristics

| Characteristic | GLS > -20% | LA max. vol. index >34 mL | GLS > -20% and LA max. vol. index >34 mL |
|---|---|---|---|
| Age, years | 48 ± 10 | 48 ± 11 | 50 ± 11 |
| PASI | 3 ± 4 | 3 ± 3 | 3,7 ± 4,5 |
| Evolution Psoriasis, years | 21 ± 13 | 22 ± 14 | 20 ± 15 |
| BMI $kg/m^2$ | 29 ± 5 | 28 ± 4 | 28,7 ± 4,1 |
| Abdominal Perimeter, cm | 100 ± 12 | 95 ± 12 | 99 ± 12 |
| Systolic BP, mmHg | 135 ± 14 | 128 ± 14 | 135 ± 13 |
| Diastolic BP, mmHg | 84 ± 8 | 79 ± 10 | 83 ± 10 |

*PASI, Psoriasis Area and Severity Index; BMI, Body Mass Index; BP, Blood Pressure; GLS, Global Longitudinal Strain; LA max. vol. index, LA Maximum Volume Index.*

Table 5. Analytic Data According to Echocardiographic Characteristics

| Characteristic | GLS > -20% | LA max. vol. index >34 mL | GLS > -20% and LA max. vol. index >34 mL |
|---|---|---|---|
| LDL, mg/dL | 136 ± 39 | 122 ±37 | 144 ± 45 |
| HDL, mg/dL | 51 ± 13 | 49 ± 12 | 48 ± 9 |
| Total Cholesterol, mg/dL | 211 ± 45 | 194 ± 42 | 215 ± 52 |
| Triglycerides, mg/dL | 121 ± 64 | 116 ± 75 | 115 ± 34 |
| Apolipoprotein B, mg/dL | 111 ± 22 | 104 ± 24 | 113 ± 29 |
| NT-proBNP, pg/mL | 15,6 ± 12 | 48 ± 43 | 20,3 ± 14,3 |
| C3, mg/dL | 121,6 ± 22,9 | 108 ± 19 | 114,7 ± 22,5 |
| hsCRP, mg/L | 4 ± 4,4 | 4,4 ± 4,3 | 6,2 ± 5,4 |
| HbA1c, % | 5,3 ± 0,4 | 5,3 ± 0,4 | 5,3 ± 0,4 |

*LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; C3, Complement Component 3; HsCRP, High-Sensitive C-Reactive Protein; HbA1c, Glycated hemoglobin; GLS, Global Longitudinal Strain; LA max. vol. index, LA Maximum Volume Index.*

## 8. Figures

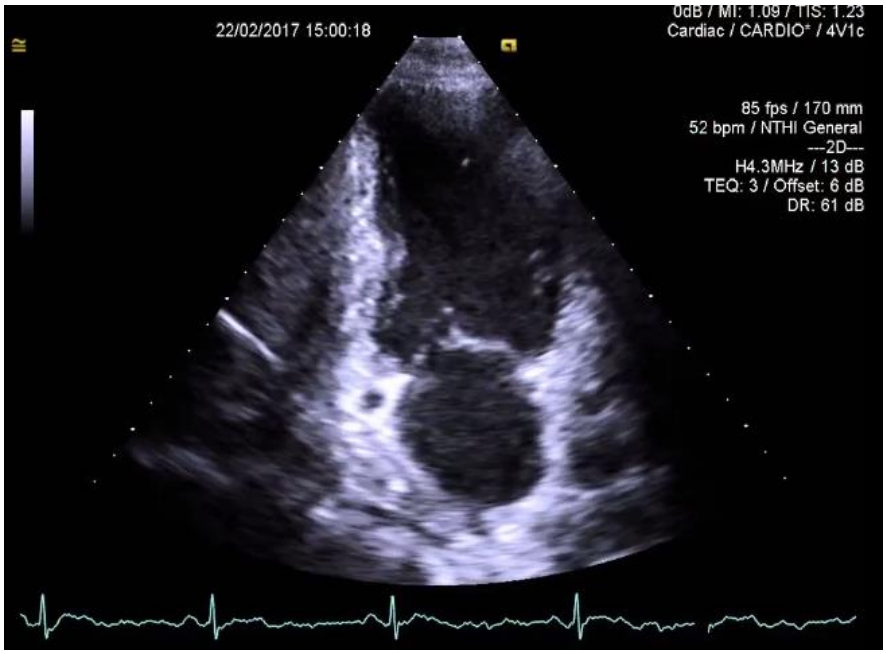


*Figure 1 Apical two-chamber view.*

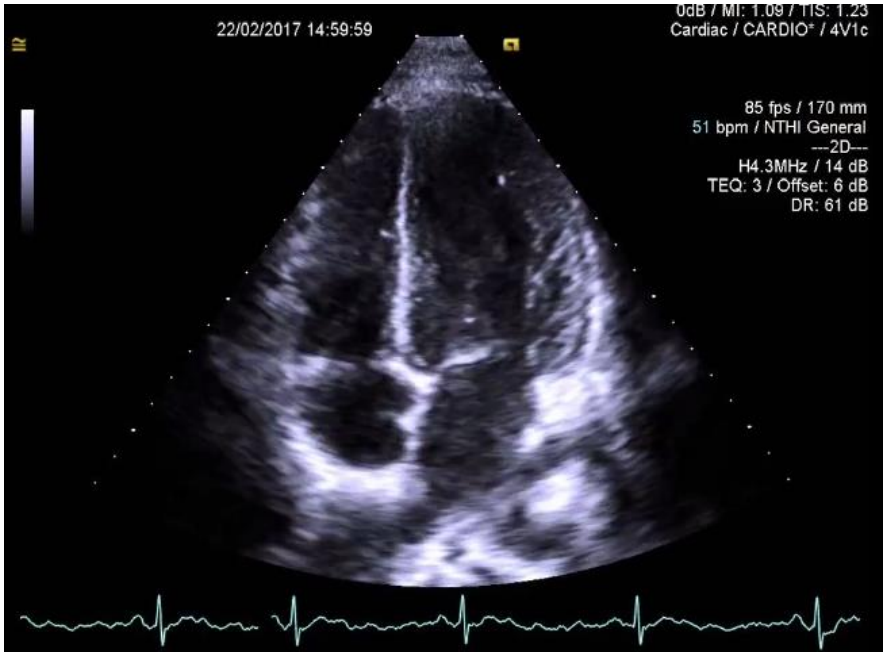


*Figure 2 Apical four-chamber view.*

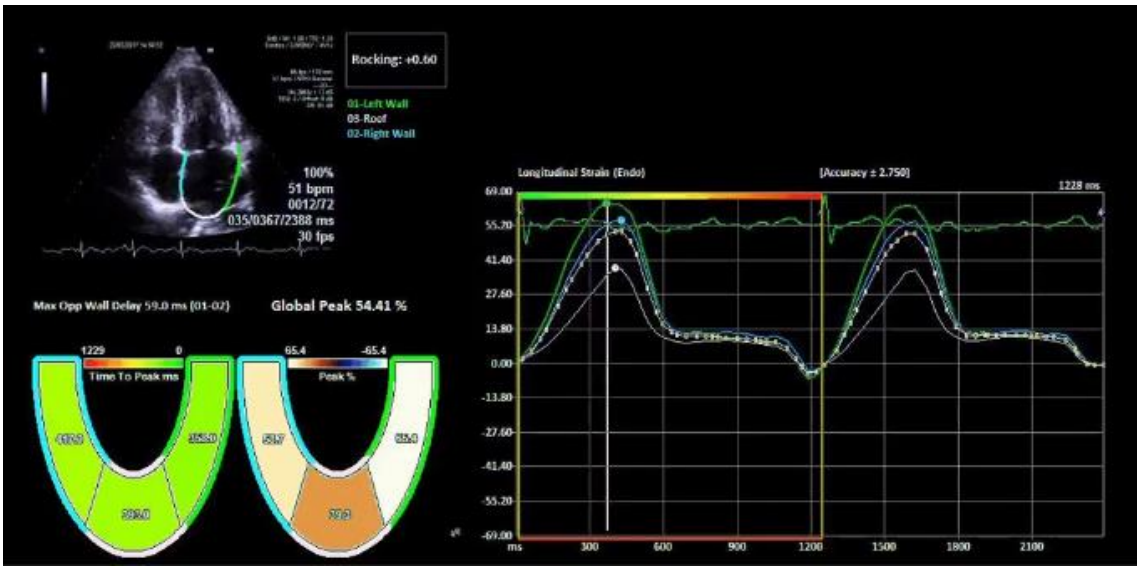


*Figure 3 Apical chamber view, longitudinal strain curve of the Left Auricle by speckle tracking echocardiography.*